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Direct Synthesis of Pyrazolo[5,1-*a*]isoindoles *via* Intramolecular Palladium-Catalyzed C–H Bond Activation

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Dedicated to Professor Bong Young Chung on the occasion of his honorable retirement.

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Abstract: An efficient, direct synthesis of pyrazolo[5,1-*a*]isoindoles employing a palladium-catalyzed intramolecular C–H bond activation of 1-(2-halobenzyl)pyrazoles has been developed. The use of lithium chloride (LiCl) was found to be essential in these reactions, to suppress further C–H bond activation at the C-3 position of pyrazolo[5,1-*a*]isoindole, when C-3 is unsubstituted. This protocol can be applied to the synthesis of a pyrazolo[5,1-*a*]isoquinoline possessing a six-membered central ring system and a fully substituted pyrazolo[5,1-*a*]isoindole using sequential intra- and intermolecular C–H bond activation.

Keywords: C–H activation; direct arylation; palladium; pyrazoles

Introduction

One of the most attractive methods for forming C–C bonds with a catalytic system is through C–H bond functionalization.[1] Transition metal-catalyzed transformations represent a central strategy in this respect, and Pd-catalyzed reactions in particular play a pivotal role.[2,3] In connection with our ongoing studies on the synthesis of biologically important heterocyclic compounds containing a pyrazole motif,[4] we became interested in exploring the intramolecular C–H bond activation of pyrazole scaffolds. Pyrazoles display a wide variety of pharmacological and agrochemical effects, including anti-inflammatory (celecoxib),[5] anti-obesity (rimonabant),[6] phosphodiesterase inhibitory (sildenafil),[7] and insecticidal (chloantraniliprole)[8] activities (Figure 1).

Although elegant approaches towards C–H bond activation in these systems have been developed by the groups of Sames[9] and the Lautens,[10] intramolecular C–H bond activation of pyrazole motifs remains somewhat limited. For example, an unsuccessful attempt at the intramolecular cyclization of pyrazole **1a** has been reported by Mori and co-workers (Scheme 1).[11] In this example, the metal-catalyzed intramolecular cyclization of 1-(2-iodobenzyl)pyrazole (**1a**) was difficult owing to the formation of the

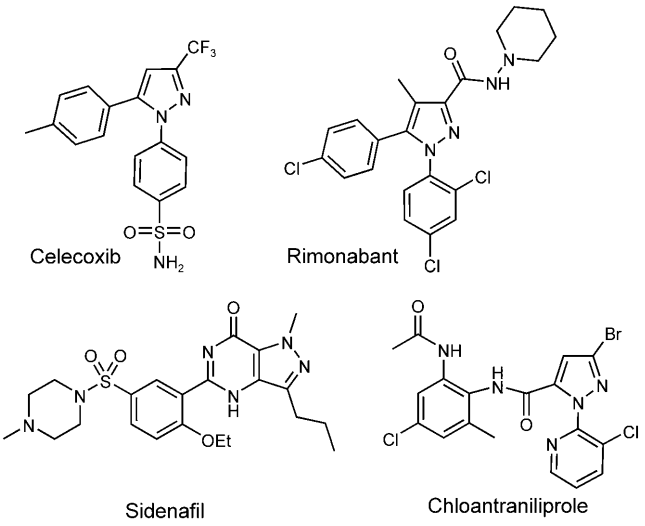
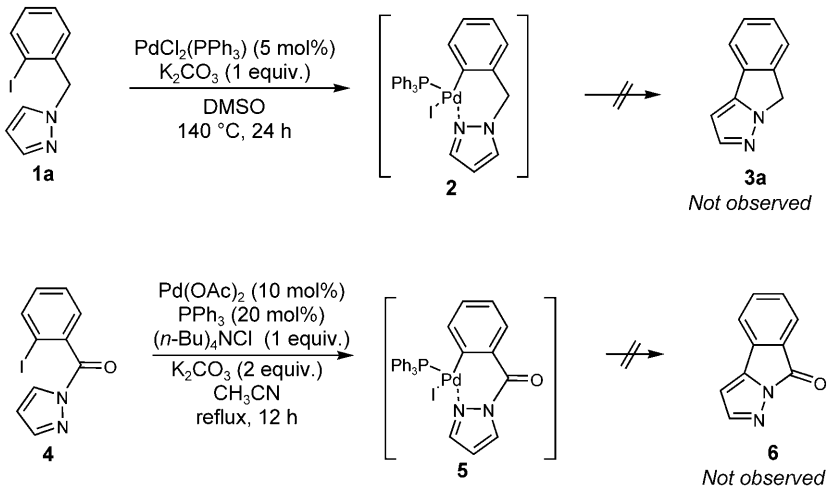


Figure 1. Biologically active compounds possessing a pyrazole motif.



Scheme 1. Catalytic poisoning of the Pd-pyrazole complex.

strongly chelating complex **2** with a basic pyrazole nitrogen atom.[12] In addition, Grigg and co-workers reported that pyrazole **4** failed to cyclize probably due to formation of a stable intermediate **5** (Scheme 1).[13] Despite these formidable challenges, the need remains for the development of novel catalytic systems that probe intramolecular C–H bond activation of pyrazoles.[14]

Recently, studies in our laboratory have concentrated on routes for the synthesis of novel polycyclic substances that are based on a Pd-catalyzed coupling and intramolecular cyclization strategy.[15] Herein, we report the first direct, one-step synthesis of pyrazolo-[5,1-*a*]isoindoles *via* Pd-catalyzed intramolecular C–H bond activation of 1-(2-halobenzyl)pyrazoles.

Results and Discussion

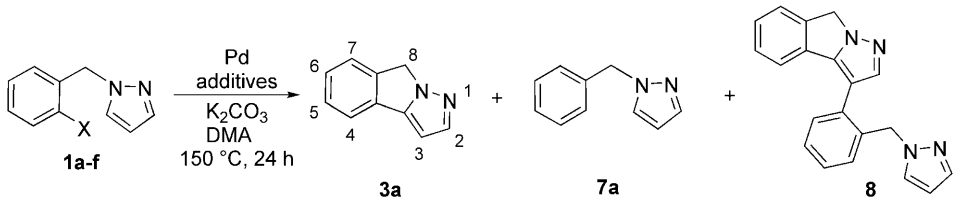
To explore this approach, we began with a model system studying the Pd-catalyzed intramolecular C–H bond activation of 1-(2-bromobenzyl)pyrazole (**1b**) for the synthesis of pyrazolo[5,1-*a*]isoindole (**3a**). The results are illustrated in Table 1. We initially employed common catalytic conditions in the presence of $Pd(OAc)_2$ (10 mol%) and K_2CO_3 (2 equiv.), using *N*,*N*-dimethylacetamide (DMA) as the solvent at 150 °C for 24 h. Using these conditions, we could obtain the desired cyclized product **3a** in moderate yield, along with the debrominated product **7a** (entry 1). Surprisingly, the heterodimeric product **8** was also observed, presumably due to further C–H bond activation of **3a** with **1b**. Although we screened several different solvents and various reaction temperatures employing this Pd catalyst, the results remained unsatisfactory. The use of pivalic acid (PivOH, 30 mol%) did not provide any benefit (entry 2). However, the addition of LiCl (3 equiv.) improved the reaction yield while suppressing the formation of heterodimer **8** (entry 3).[16]

We were pleased to find that the combination of PivOH and LiCl significantly enhanced the reaction, achieving a 71% isolated yield (entry 4). Additionally, we found that decreasing the amount of LiCl (1 equiv.) slightly decreased the yield, while increasing the amount of LiCl (5 equiv.) significantly lowered the yields (entries 5 and 6). Other additives that were tested, including Ag_2CO_3 and Ag(OAc), also proved inferior to our previous experiments using LiCl (entries 7 and 8). The addition of AcOH in place of the PivOH resulted in comparable results, affording **3a** in 67% yield (entry 9). When the reaction temperature was lowered to 100 °C, only 14% and 6% of the desired product were observed with respect to bromo- and chloroarene (entry 10 and entry 13).

We next investigated the scope of different halogen substituents on the aryl ring by replacing the bromoarene that we had previously been using with a chloro- or iodoarene. Interestingly, chloroarene **1c**, in the presence of PivOH, proved effective and reduced heterodimer formation (entry 11). In contrast, the use of PivOH and LiCl significantly retarded the reaction process (entry 12). Furthermore, iodoarene **1a** resulted in a similar product ratio as that of bromoarene **1b** (entries 14 and 15). Based on these observations, we hypothesized that the salt effect of LiCl could control the formation of heterodimeric compound **8**. Using sulfonate-based ring substituents, such as tosylate, mesylate, and triflate, provided unsatisfactory results (entries 16–18).

The use of a wide range of phosphine-based ligands (Figure 2) did not exert any notable influence on the reaction yield, as illustrated in Table 2. Neither monophosphine biaryl ligands[17] **L1**–**L5** (entries 1–5) nor bidentate ligands **L6**–**L8** (entries 6–8) gave satisfactory results. Pyrrole- and indole-based ligands[18] **L9**–**L11**

Table 1. Formation of pyrazolo[5,1-*a*]isoindole under various reaction conditions.[a]



Entry	X	Additives	Yield [%][b]		
			3a	**7a**	**8**
1	Br (**1b**)	none	53	6	41
2	Br (**1b**)	PivOH (30 mol%)	55	5	40
3	Br (**1b**)	LiCl (3 equiv.)	65	20	10
4	Br (**1b**)	PivOH (30 mol%) + LiCl (3 equiv.)	75 (71)[c]	15	10
5	Br (**1b**)	PivOH (30 mol%) + LiCl (1 equiv.)	67	7	26
6	Br (**1b**)	PivOH (30 mol%) + LiCl (5 equiv.)	10	10	0
7	Br (**1b**)	PivOH (30 mol%) + Ag_2CO_3 (1 equiv.)	0	20	0
8	Br (**1b**)	PivOH (30 mol%) + Ag(OAc) (1 equiv.)	26	15	0
9	Br (**1b**)	AcOH (30 mol%) + LiCl (3 equiv.)	67	13	20
10[d]	Br (**1b**)	PivOH (30 mol%) + LiCl (3 equiv.)	14	4	4
11	Cl (**1c**)	PivOH (30 mol%)	69	3	10
12	Cl (**1c**)	PivOH (30 mol%) + LiCl (3 equiv.)	45	13	5
13[d]	Cl (**1c**)	PivOH (30 mol%) + LiCl (3 equiv.)	6	0	2
14	I (**1a**)	PivOH (30 mol%)	60	4	36
15	I (**1a**)	PivOH (30 mol%) + LiCl (3 equiv.)	65	25	10
16[e]	OTs (**1d**)	PivOH (30 mol%) + LiCl (3 equiv.)	2	2	–
17[e]	OMs (**1e**)	PivOH (30 mol%) + LiCl (3 equiv.)	4	4	–
18[e]	OTf (**1f**)	PivOH (30 mol%) + LiCl (3 equiv.)	13 (14)[c]	9	–

[a] *Conditions:* **1** (1 mmol), $Pd(OAc)_2$ (10 mol%), K_2CO_3 (2 equiv.), additives, DMA (0.14 M), 150 °C, 24 h.
[b] Yields determined by ^1H NMR.
[c] Isolated yields in parenthesis.
[d] The reaction was performed at 100 °C.
[e] Starting sulfonates were decomposed to the corresponding phenol.

(entries 9–11) proved inferior in circumventing the formation of heterodimer **8**. Consequently, the reaction under phosphine ligand-free conditions was used as the optimized catalytic system.

Next, we wanted to investigate the influence of LiCl in these reactions with greater detail. To prevent the formation of the heterodimeric by-product, we used 4-methylpyrazole **1g**, in which the C-3 position of the product **3b** is blocked for the further C–H bond activation, as a precursor. As shown in Table 3, the reaction was found to be dependent on the amount of LiCl used. When the LiCl was used in

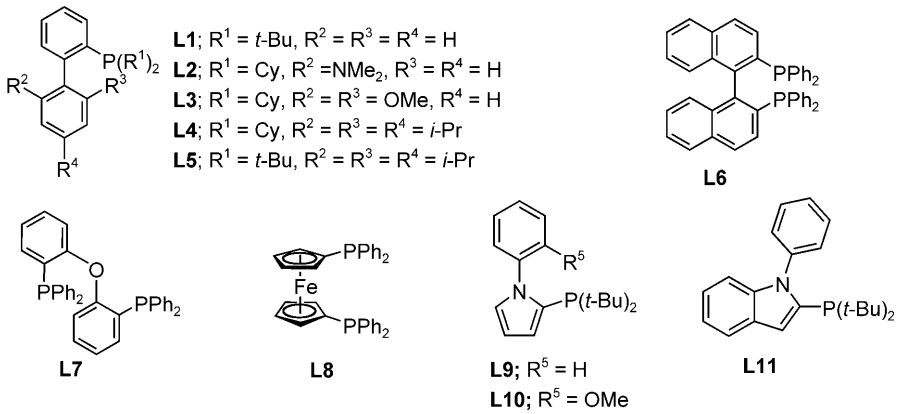


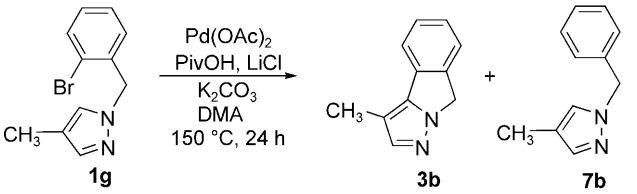
Figure 2. Structure of phosphine ligands.

Table 2. Ligand screening.[a]

Entry	Ligand	Yield [%][b]		
		3a	**7a**	**8**
1	**L1**	49	7	14
2	**L2**	69	5	24
3	**L3**	61	6	28
4	**L4**	74	7	19
5	**L5**	69	4	27
6	**L6**	69	6	25
7	**L7**	62	6	26
8	**L8**	56	25	18
9	**L9**	61	7	26
10	**L10**	63	5	26
11	**L11**	67	7	26

[a] *Conditions:* **1b** (1 mmol), $Pd(OAc)_2$ (10 mol%), ligand (20 mol%), PivOH (30 mol%), LiCl (3 equiv.), K_2CO_3 (2 equiv.), DMA (0.14 M), 150 °C, 24 h.
[b] Yields determined by ^1H NMR.

Table 3. Formation of 3-methylpyrazolo[5,1-*a*]isoindole.[a]



Entry	LiCl (equiv.)	Yield [%][b]	
		3b	**7b**
1	none	100 (87)[c]	0
2	1	100	0
3	2	100	0
4	3	99 (86)[c]	1
5	4	71	29
6	5	52	48

[a] *Conditions:* **1g** (1 mmol), $Pd(OAc)_2$ (10 mol%), PivOH (30 mol%), LiCl (0–5 equiv.), K_2CO_3 (2 equiv.), DMA (0.14 M), 150 °C, 24 h.
[b] Yields determined by ^1H NMR.
[c] Isolated yields in parenthesis.

equivalents greater than 3, the reaction became sluggish and resulted in a lower yield (entries 4 and 5). In contrast, with the absence of LiCl, the reaction proceeded smoothly to provide the cyclised product **3b** with 100% conversion (entry 1). We believe that these results illustrate that the primary purpose of LiCl addition is to minimize the formation of the by-product.

We subsequently adopted these optimized conditions, including $Pd(OAc)_2$ (10 mol%), PivOH (30 mol%), LiCl (none or 3 equiv.), and K_2CO_3 (2 equiv.) in DMA at 150 °C for 6 h, for the synthesis of various pyrazolo[5,1-*a*]isoindoles using a wide range of substituted pyrazole-benzyl halides as precursors (Table 4). The use of LiCl was mainly dependent on the substitution pattern of pyrazole. For example, in the absence of LiCl, 4-methylpyrazole **1g** provided the desired product **3b** in 87% yield. However, in the case of compound **1h**, which was bearing a 3-methylpyrazole group, LiCl was required to bring the reaction to completion to produce the corresponding pyrazoloisoindole **3c** in 99% yield (entry 2). Aryl-substituted pyrazoles **1i** and **1j** also resulted in the corresponding cyclized products **3d** and **3e** in 84% and 85% yield, respectively (entries 3 and 4). The structure of **3e** was confirmed by X-ray crystallography (see ORTEP representation in Figure 3). It should be noted that in cases using C-3-substituted pyrazoles, little to no heterodimeric side product was observed. In case of the disubstituted pyrazole **1k**, the reaction provided solely **3f** in good yield (entry 5).

In the case of the N-2 substituted indazole **1l**, we successfully prepared isoindolo[2,1-*b*]indazole **3g** in moderate yield. Greaney and co-workers had previously reported that this type of intramolecular cyclization was ineffective under their optimized conditions [$Pd(dppf)_2Cl_2$·DCM, PPh_3, Ag_2CO_3, H_2O, 50 °C, 16 h].[19] Both electron-donating and electron-withdrawing substituents on the bromoarene were tolerated, providing the desired products in good yields (entries 7–9). Sterically hindered bromoarene **1p** was also a good substrate for cyclization and provided 3,4-dimethyl-substituted pyrazoloisoindole **3k** in 97% yield (entry 10). In addition, heteroarenes, such as naphthyl, thienyl, and pyridinyl moieties, afforded the corresponding products, albeit reaction yields were only moderate (entries 11–13). Interestingly, when the reaction of bromothiophene **1r** was carried out in the absence of LiCl, the further C-5 dimerization of **3m** with **1r** occurred significantly to afford compound **12**[21] along with the desired product **3m** in only 17% yield (entry 12).

To expand the utility of this reaction protocol, we reacted 2-bromophenethylpyrazole **9** under standard conditions to provide 5,6-dihydropyrazolo[5,1-*a*]isoquinoline **10** possessing a six-membered central ring system in 63% yield (Scheme 2). Furthermore, the last available C–H bond activation at the C-3 position of **3e** was achieved in the presence of $P(n\text{-Bu})Ad_2$ to provide the fully substituted pyrazolo[5,1-*a*]isoindole **11** in 65% yield.[22]

Conclusions

In summary, we have established a novel, direct, one-step synthesis of pyrazolo[5,1-*a*]isoindoles *via* Pd-catalyzed intramolecular C–H bond activation. The use of LiCl is essential in these reactions to suppress further

Table 4. Scope of intramolecular Pd-catalyzed C–H bond activation.[a]

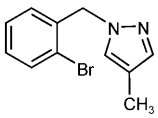
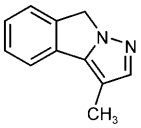
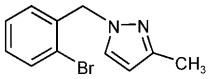
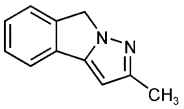
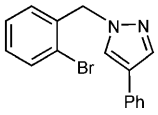
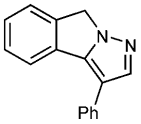
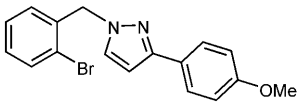
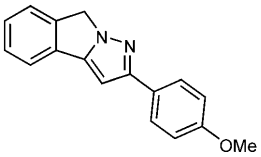
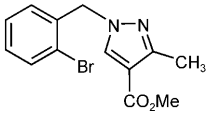
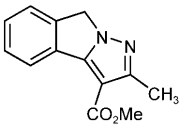
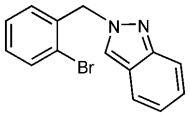
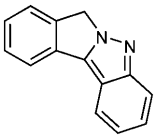
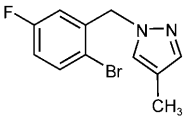
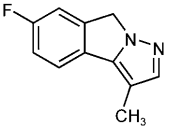
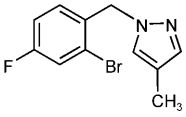
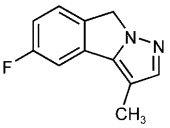
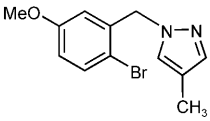
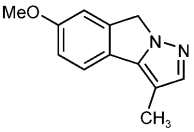
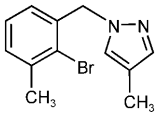
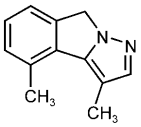
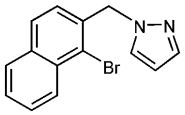
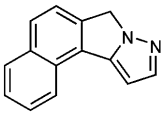
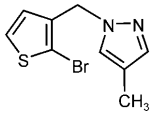
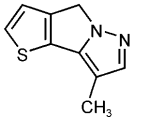
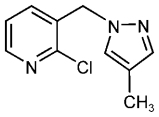
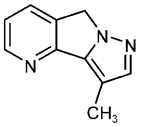
Entry	Substrate		LiCl (equiv.)	Product		Yield [%][b]
1		**1g**	none		**3b**	87
2		**1h**	3.0		**3c**	99
3		**1i**	none		**3d**	84
4		**1j**	3.0		**3e**	85
5		**1k**	none		**3f**	78
6		**1l**	none		**3g**	53
7		**1m**	none		**3h**	79
8		**1n**	none		**3i**	85
9		**1o**	none		**3j**	85
10		**1p**	none		**3k**	97
11		**1q**	3.0		**3l**	50
12		**1r**	3.0		**3m**	51 (17)[c]

Table 4. (Continued)

Entry	Substrate	LiCl (equiv.)	Product	Yield [%][b]
13	 **1s**	none	 **3n**	55

[a] *Reaction conditions:* substrate (1 mmol), $Pd(OAc)_2$ (10 mol%), PivOH (30 mol%), LiCl (0 or 3 equiv.), K_2CO_3 (2 equiv.), DMA (0.14 M), 150 °C, 6 h.
[b] Isolated yields.
[c] Isolated yield when the reaction was performed in the absence of LiCl.

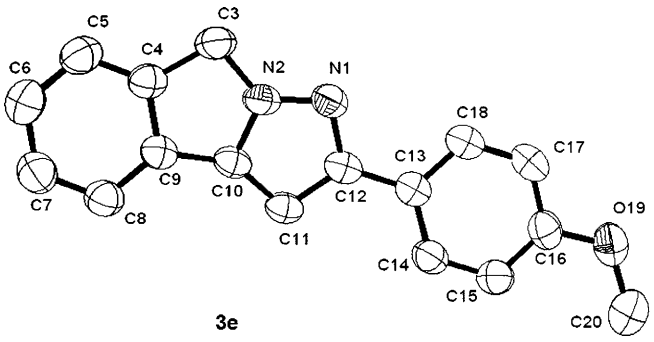
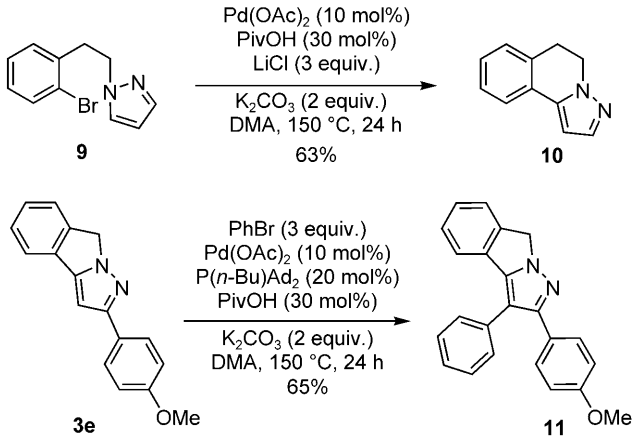


Figure 3. ORTEP representation of pyrazolo[5,1-*a*]isoindole **3e**. Thermal ellipsoids are set at 50% probability.[20]



Scheme 2. Synthesis of pyrazolo[5,1-*a*]isoquinoline **10** and fully substituted pyrazolo[5,1-*a*]isoindole **11**.

C–H bond activation at the C-3 position of pyrazolo-[5,1-*a*]isoindole when the pyrazole is unsubstituted. Furthermore, we have applied this protocol to the synthesis of pyrazolo[5,1-*a*]isoquinolines possessing a six-membered central ring system. Fully substituted pyrazolo[5,1-*a*]isoindole was also synthesized by using sequential intra- and intermolecular C–H bond activation. Further studies towards the synthesis of biologically important compounds will be discussed in following reports.

Experimental Section

Typical Procedure for the Synthesis of 8*H*-Pyrazolo[5,1-*a*]isoindoles 3 in the Presence of LiCl

A vial was charged with 1-(2-halobenzyl)-1*H*-pyrazole (0.50 mmol), $Pd(OAc)_2$ (11 mg, 10 mol%), K_2CO_3 (138 mg, 1.0 mmol), and LiCl (64 mg, 1.5 mmol). A solution of PivOH (15 mg, 30 mol%) in DMA (3.6 mL, 0.14 M) was added. The resulting mixture was vigorously stirred at 150 °C for 6 h. The reaction mixture was cooled to room temperature and directly purified by silica gel column chromatography (10% EtOAc/hexanes) to provide the corresponding isoindoles **3a**–**3n**.

8*H*-Pyrazolo[5,1-*a*]isoindole (3a): 24 h; yield: 71%, yellow solid, mp 43–45 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65 (d, 1H, J = 1.8 Hz), 7.59 (d, 1H, J = 7.5 Hz), 7.47 (d, 1H, J = 7.4 Hz), 7.41 (d, 1H, J = 7.2 Hz), 7.33 (t, 1H, J = 7.3 Hz), 6.38 (d, 1H, J = 1.8 Hz), 5.12 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.3, 143.6, 140.5, 131.0, 128.2, 127.2, 123.5, 120.5, 96.4, 52.1; IR (neat): ν = 1474, 1452, 1401, 1316, 932, 749 cm^{-1}; MS (EI): m/z = 156 (M^+, 100), 129 (99), 102 (35), 77 (21), 63(27); HR-MS (EI): m/z = 156.0678, calcd. for $C_{10}H_8N_2$ [M^+]: 156.0687.

3-{2-[(1*H*-Pyrazol-1-yl)methyl]phenyl}-8*H*-pyrazolo[5,1-*a*]isoindole (8): colorless liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.52 (s, 1H), 7.50 (d, 1H, J = 1.6 Hz), 7.50–7.46 (m, 2H), 7.39 (td, 1H, J = 7.5, 1.4 Hz), 7.37–7.30 (m, 4H), 7.19 (d, 1H, J = 2.2 Hz), 7.12 (d, 1H, J = 7.5 Hz), 6.19 (t, 1H, J = 2.1 Hz), 5.40 (s, 2H), 5.18 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.8, 143.3, 140.6, 139.5, 135.1, 131.7, 130.7, 129.4, 128.8, 128.3, 128.11, 128.06, 127.6, 123.6, 120.2, 112.4, 105.8, 53.7, 52.3, 29.7; IR (neat): ν = 1605, 1585, 1402, 1394, 1087, 1047, 753, 726 cm^{-1}; MS (EI): m/z = 312 (M^+, 1), 244 (1), 111 (8), 97 (14), 57 (100); HR-MS (EI): m/z = 312.1364, calcd. for $C_{20}H_{16}N_4$ [M^+]: 312.1375.

3-Methyl-8*H*-pyrazolo[5,1-*a*]isoindole (3b): The reaction was run without LiCl. Yield: 87%, white solid, mp 96–97 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59 (d, 1H, J = 7.6 Hz), 7.45–7.38 (m, 3H), 7.31 (d, 1H, 7.5 Hz), 5.07 (s, 2H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.0, 143.6, 140.2, 131.7, 128.1, 126.6, 123.5, 119.8, 107.9, 52.0, 8.8; IR (neat): ν = 1477, 1546, 1402, 1382, 1321, 1160, 1004, 761, 717 cm^{-1}; MS (EI): m/z = 170 (M^+, 100), 155 (16), 143 (27), 115 (29),

89 (11); HR-MS (EI): m/z = 170.0840, calcd. for $C_{11}H_{10}N_2$ [M^+]: 170.0844.

2-Methyl-8*H*-pyrazolo[5,1-*a*]isoindole (3c): Yield: 99%, white solid, mp 67–68 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54 (d, 1H, J = 7.5 Hz), 7.45–7.26 (m, 4H), 6.16 (s, 2H), 5.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.3, 147.0, 140.4, 131.3, 128.1, 127.0, 123.4, 120.4, 95.9, 52.0, 14.4; IR (neat): ν = 1730, 1562, 1469, 1004, 754, 717 cm^{-1}; MS (EI): m/z = 170 (M^+, 100), 155(26), 129 (77), 115 (35), 63 (25); HR-MS (EI): m/z = 170.0840, calcd. for $C_{11}H_{10}N_2$ [M^+]: 170.0844.

3-Phenyl-8*H*-pyrazolo[5,1-*a*]isoindole (3d): The reaction was run without LiCl. Yield: 84%, white solid, mp 98–99 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (d, 1H, J = 6.7 Hz), 7.77 (s, 1H), 7.63 (d, 2H, J = 7.1 Hz), 7.47 (t, 3H, J = 7.7 Hz), 7.41–7.30 (m, 3H), 5.17 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3, 156.0, 147.5, 140.3, 131.1, 128.2, 127.3, 126.9, 126.7, 123.5, 120.5, 114.1, 92.9, 55.3, 52.3; IR (neat): ν = 1606, 1473, 1454, 1353, 1236, 1170, 965, 755, 697 cm^{-1}; MS (EI): m/z = 232 (M^+, 100), 204 (51), 176 (20), 88 (12); HR-MS (EI): m/z = 232.0995, calcd. for $C_{16}H_{12}N_2$ [M^+]: 232.1000.

2-(4-Methoxyphenyl)-8*H*-pyrazolo[5,1-*a*]isoindole (3e): Yield: 85%, white solid, mp 171–172 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (d, 2H, J = 8.9 Hz), 7.61 (d, 1H , J = 7.4 Hz), 7.48 (d, 1H, J = 7.4 Hz), 7.42 (td, 1H, J = 7.5, 1.2 Hz), 7.34 (td, 1H, J = 7.5, 1.2 Hz), 6.96 (d, 2H, J = 8.9 Hz), 5.15 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4, 156.0, 147.5, 140.3, 131.1, 128.3, 127.3, 126.9, 126.8, 123.5, 120.5, 114.1, 92.9, 55.3, 52.3; IR (neat): ν = 2111, 1610, 1527, 1453, 1432, 1298, 1245, 1182, 1029, 837, 758 cm^{-1}; MS (EI): m/z = 262 (M^+, 100), 247 (42), 189 (23), 129 (22), 63 (21); HR-MS (EI): m/z = 262.1104, calcd. for $C_{17}H_{14}N_2O$ [M^+]: 262.1106.

Methyl 2-methyl-8*H*-pyrazolo[5,1-*a*]isoindole-3-carboxylate (3f): The reaction was run without LiCl. Yield: 78%, white solid, mp 58–60 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27 (d, 1H, J = 7.1 Hz), 7.51–7.41 (m, 3H), 5.07 (s, 2H), 3.96 (s, 3H), 2.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.6, 155.8, 149.5, 141.0, 130.4, 128.5, 123.7, 123.1, 104.3, 52.3, 51.1, 14.6; IR (neat): ν = 1693, 1556, 1472, 1443, 1278, 1198, 1164, 1111, 1086, 768, 722 cm^{-1}; MS (EI): m/z = 228 (M^+, 68), 213 (24), 197 (100), 115 (24); HR-MS (EI): m/z = 228.0895, calcd. for $C_{13}H_{12}N_2O_2$ [M^+]: 228.0899.

3*H*-Isoindolo[2,1-*b*]indazole (3g): The reaction was run without LiCl. Yield: 53%, white solid, mp 118–200 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, 1H, J = 8.4 Hz), 7.83–7.75 (m, 2H), 7.36 (t, 2H, J = 7.7 Hz), 7.19 (t, 1H, J = 7.5 Hz), 5.38 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.4, 139.5, 139.2, 131.6, 128.6, 126.8, 126.1, 123.4, 121.6, 119.8, 119.7, 118.0, 114.7, 53.3; IR (neat): ν = 1737, 1689, 1476, 1399, 1379, 1318, 1280, 1011, 752, 715 cm^{-1}; MS (EI): m/z = 206 (M^+, 100), 179 (19), 151 (24), 103 (15), 89 (16); HR-MS (EI): m/z = 206.0835, calcd. for $C_{14}H_{10}N_2$ [M^+]: 206.0844.

6-Fluoro-3-methyl-8*H*-pyrazolo[5,1-*a*]isoindole (3h): The reaction was run without LiCl. Yield: 79%, white solid, mp 115–116 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52 (dd, 1H, J = 8.3, 4.9 Hz), 7.41 (s, 1H), 7.18–7.08 (m, 2H), 5.06 (s, 2H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.80 (d, J = 246.0 Hz), 144.1, 142.9, 142.2 (d, J = 8.9 Hz), 127.9 (d, J = 2.8 Hz), 120.8 (d, J = 8.8 Hz), 115.2 (d, J = 22.9 Hz), 111.6 (d, J = 24.6 Hz), 107.6, 52.0 (d, J = 2.8 Hz), 8.7; IR (neat): ν = 1595, 1475, 1447, 1430, 1400, 1246, 1206, 1161, 1126, 808 cm^{-1}; MS (EI): m/z = 188 (M^+, 100), 173 (11), 161 (25), 133 (31), 107 (11); HR-MS (EI): m/z = 188.0747, calcd. for $C_{14}H_{10}N_2$ [M^+]: 206.0844.

5-Fluoro-3-methyl-8*H*-pyrazolo[5,1-*a*]isoindole (3i): The reaction was run without LiCl. Yield: 85%, yellow solid, mp 119–120 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44 (s, 1H), 7.38 (dd, 1H, J = 8.1, 4.7 Hz), 7.28–7.25 (m, 1H), 7.02–6.96 (m ,1H), 5.04 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.0 (d, J = 245.2 Hz), 144.1, 142.8 (d, J = 3.5 Hz), 135.4 (d, J = 2.8 Hz), 133.3 (d, J = 10.0 Hz), 124.6 (d, J = 9.1 Hz), 113.3 (d, J = 23.1 Hz), 107.3 (d, J = 24.8 Hz), 51.7, 8.72; IR (neat): ν = 1595, 1476, 1431, 1400, 1276, 1247, 1206, 1090, 809 cm^{-1}; MS (EI): m/z = 188 (M^+, 1), 129 (18), 97 (23), 73 (100); HR-MS (EI): m/z = 188.0747, calcd. for $C_{11}H_9FN_2$ [M^+]: 188.0750.

6-Methoxy-3-methyl-8*H*-pyrazolo[5,1-*a*]isoindole (3j): The reaction was run without LiCl. Yield: 85%, white solid, mp 90–92 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (d, 1H, J = 8.3 Hz), 7.39 (s, 1H), 7.00 (d, 1H, J = 2.1 Hz), 6.92 (dd, 1H, J = 8.3, 2.3 Hz), 5.02 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.9, 143.9, 143.6, 142.1, 124.6, 120.5, 113.4, 110.0, 106.7, 55.6, 52.0, 8.8; IR (neat): ν = 1712, 1400, 1481, 1289, 1265, 1253, 1216, 1141, 1038, 1000, 807, 675 cm^{-1}; MS (EI): m/z = 200 (M^+, 100), 185 (41), 130 (32), 103 (26), 77 (27); HR-MS (EI): m/z = 200.0948, calcd. for $C_{12}H_{12}N_2O$ [M^+]: 200.0950.

3,4-Dimethyl-8*H*-pyrazolo[5,1-*a*]isoindole (3k): The reaction was run without LiCl. Yield: 97%, yellow solid, mp 87–89 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (s, 1H), 7.26–7.14 (m, 4H), 5.02 (s, 2H), 2.66 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.0, 143.9, 140.3, 131.6, 130.5, 129.9, 127.0, 120.7, 107.7, 51.8, 21.8, 11.3; IR (neat): ν = 1760, 1484, 1450, 1394, 1347, 1321, 1275, 1156, 836, 806, 763, 673 cm^{-1}; MS (EI): m/z = 184 (M^+, 100), 169 (71), 157 (14), 142 (14), 128 (14), 115 (15); HR-MS (EI): m/z = 184.1027, calcd. for $C_{12}H_{12}N_2$ [M^+]: 184.1000.

10*H*-Pyrazolo[1′,5′:1,2]pyrrolo[3,4-*b*]naphthalene (3l): Yield: 50%, yellow solid, mp 102–103 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.21 (d, 1H, J = 8.3 Hz), 7.95 (d, 1H, J = 8.2 Hz), 7.87 (d, 1H, J = 8.5 Hz), 7.68–7.57 (m, 3H), 6.678 (s, 1H), 5.26 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.1, 143.8, 138.3, 133.2, 128.7, 127.9, 127.6, 127.1, 126.6, 126.3, 124.1, 121.0, 97.8, 52.7; IR (neat): ν = 1553, 1378, 1522, 1369, 1173, 956, 805, 779 cm^{-1}; MS (EI): m/z = 206 (M^+, 100), 179 (38), 152 (34); HR-MS (EI): m/z = 206.0847, calcd. for $C_{14}H_{10}N_2$ [M^+]. 206.0844.

3-Methyl-7*H*-thieno[2′,3′:3,4]pyrrolo[1,2-*b*]pyrazole (3m): Yield: 51%, yellow solid, mp 114–115 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37 (s, 1H), 7.34 (d, 1H, J = 4.9 Hz), 7.07 (d, 1H, J = 4.9 Hz), 4.95 (s, 3H), 2.21 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.6, 143.2, 141.0, 131.5, 127.3, 121.5, 105.7, 51.4, 8.8; IR (neat): ν = 1727, 1602, 1444, 1395, 1383, 1326, 1263, 1085, 1008, 822, 708, 675 cm^{-1}; MS (EI): m/z = 176 (M^+, 100), 161 (12), 149 (20), 121 (13), 108 (9); HR-MS (EI): m/z = 176.0398, calcd. for $C_9H_8N_2S$ [M^+]: 176.0408.

3-Methyl-8*H*-pyrazolo[1′,5′:1,2]pyrrolo[3,4-*b*]pyridine (3n): The reaction was run without LiCl. Yield: 55%, yellow solid, mp 152–153 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.59 (d, 1H, J = 5.1 Hz), 7.72 (d, 1H, J = 7.7 Hz), 7.50 (s, 1H), 7.17 (dd, 1H, J = 7.7, 5.1 Hz), 5.10 (s, 2H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.1, 149.4, 144.6, 142.4,

134.5, 130.8, 120.6, 110.2, 50.6, 8.6; IR (neat): ν = 1599, 1574, 1390, 1175, 829, 791, 682 cm^{-1}; MS (EI): *m/z* = 171 (M^+, 100), 143 (42), 117 (16), 89 (9); HR-MS (EI): *m/z* = 171.0798, calcd. for $C_{10}H_9N_3$ [M^+]: 171.0796.

5,6-Dihydropyrazolo[5,1-*a*]isoquinoline (10)

To a vial were added 1-(2-bromophenethyl)-1*H*-pyrazole **9** (126 mg, 0.5 mmol), $Pd(OAc)_2$ (11 mg, 10 mol%), LiCl (64 mg, 1.5 mmol), and K_2CO_3 (138 mg, 1.0 mmol). A solution of PivOH (15 mg, 30 mol%) in DMA (3.6 mL, 0.14 M) was added and the reaction vial was tightly sealed. The resulting mixture was vigorously stirred at 150 °C for 24 h and then cooled to room temperature. The reaction mixture was purified by silica gel column chromatography (10% EtOAc/hexanes) to provide isoquinoline **10** as a colorless liquid; yield: 53 mg (63%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55–7.52 (m, 2H), 7.32–7.23 (m, 3H), 6.54 (d, 1H, *J* = 1.9 Hz), 4.35 (t, 2H, *J* = 6.9 Hz), 3.19 (t, 2H, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.2, 138.6, 131.7, 128.2, 128.0, 127.3, 127.0, 124.0, 100.5, 46.2, 29.2; IR (neat): ν = 1722, 1487, 1468, 1409, 1338, 1350, 1329, 753 cm^{-1}; MS (EI): *m/z* = 170 (M^+, 100), 156 (23), 142 (55), 115 (97); HR-MS (EI): *m/z* = 170.0840, calcd. for $C_{11}H_{10}N_2$ [M^+]: 170.0844.

2-(4-Methoxyphenyl)-3-phenyl-8*H*-pyrazolo[5,1-*a*]-isoindole (11)

To a vial (3 mL) were added 2-(4-methoxyphenyl)-8*H*-pyrazolo[5,1-*a*]isoindole **3e** (131 mg, 0.5 mmol), 1-bromobenzene (236 mg, 1.5 mmol), $Pd(OAc)_2$ (11 mg, 10 mol%), P(*n*-Bu)Ad_2 (36 mg, 20 mol%), and K_2CO_3 (138 mg, 1.0 mmol) sequentially. A solution of PivOH (15 mg, 30 mol%) in DMA (200 μL, 2.5 M) was added and the reaction vial was tightly sealed. The resulting mixture was vigorously stirred at 150 °C for 24 h and then cooled to room temperature. The mixture was purified by silica gel column chromatography (10% EtOAc/hexanes) to provide **11** as a white solid; yield: 110 mg (65%). mp 180–181 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55–7.53 (m, 1H), 7.46–7.29 (m, 10H), 6.83 (d, 2H, *J* = 8.8 Hz), 5.18 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 153.1, 144.7, 140.4, 133.3, 131.3, 129.7, 129.4, 128.6, 128.1, 127.4, 126.8, 126.3, 123.5, 120.1, 113.7, 112.5, 55.2, 52.2; IR (neat): ν = 2928, 1608, 1524, 1427, 1244, 834, 758, 700 cm^{-1}; MS (EI): *m/z* = 338 (M^+, 100), 323 (14), 204 (12); HR-MS (EI): *m/z* = 338.1411, calcd. for $C_{23}H_{18}N_2O$ [M^+]: 338.1419.

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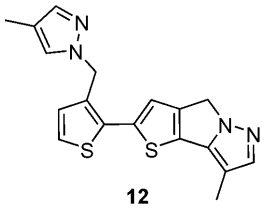
[21] Compound **12** was characterized as the dimerized product on the thiophene ring (see the Supporting Information for spectral data). For the C-2 selective direct arylation of thiophene: see ref.[2e]



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[22] We are grateful to a referee for pointing out that the pyrazole group could serve as a directing group, affording the arylated product on the anisole ring of compound **3e**. In our case of palladium-catalyzed conditions we could observe no or little anisole-substituted product. For ruthenium-catalyzed direct arylation of *N*-arylpyrazoles as a directing group, see: a) L. Ackermann, A. Althammer, R. Born, *Tetrahedron* **2008**, *64*, 6115–6124; b) L. Ackermann, A. Althammer, R. Born, *Synlett* **2007**, 2833–2836.

